NICE National Institute for Health and Care Excellence

NICE guidance

Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Daratumumab with bortezomib, lenalidomide and dexamethasone can be used as an option for untreated multiple myeloma in adults when an autologous stem cell transplant (ASCT) is unsuitable. Daratumumab can only be used if the company provides it according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with daratumumab with bortezomib, lenalidomide and dexamethasone that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Daratumumab with bortezomib, lenalidomide and dexamethasone must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Daratumumab with bortezomib, lenalidomide and dexamethasone must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that daratumumab with bortezomib, lenalidomide and dexamethasone provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why the committee made these recommendations

For this evaluation, the company asked for daratumumab with bortezomib, lenalidomide and dexamethasone to be considered only for untreated multiple myeloma in adults when an ASCT is unsuitable. This does not include everyone who it is licensed for. NICE is evaluating daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable separately.

Usual treatment for adults with untreated multiple myeloma when an ASCT is unsuitable includes:

- daratumumab plus lenalidomide and dexamethasone
- isatuximab plus bortezomib, lenalidomide and dexamethasone.

Daratumumab plus bortezomib, lenalidomide and dexamethasone has not been directly compared in a clinical trial with the usual treatments, but indirect comparisons suggest that it is likely to work as well as some of these.

Clinical trial evidence shows that daratumumab plus bortezomib, lenalidomide and dexamethasone increases how long people have before their condition gets worse and how long they live compared with bortezomib, lenalidomide and dexamethasone.

There are some uncertainties in the economic model. But, despite these uncertainties, the cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, daratumumab with bortezomib, lenalidomide and dexamethasone can be used.

2 Information about daratumumab

Marketing authorisation indication

2.1 Daratumumab (Darzalex, Johnson & Johnson) is indicated 'in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for daratumumab.

Price

2.3 The list price for daratumumab is £4,320 per 1,800 mg/15 ml vial (excluding VAT; BNF online accessed May 2026).

2.4 The company has a commercial arrangement. This makes daratumumab available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published on Johnson & Johnson's webpage on their responsibility to the planet.

3 Committee discussion

The evaluation committee considered evidence submitted by Johnson & Johnson, a review of this submission by the external assessment group (EAG) and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Multiple myeloma

3.1 Multiple myeloma is an incurable cancer of plasma cells in the bone marrow, characterised by periods of remission and relapse. The patient experts emphasised that it is a complex and highly individual condition, with symptoms that vary widely between people and in severity. They explained that living with multiple myeloma can have a substantial psychological impact because of the ongoing uncertainty and constant possibility of relapse. With each relapse, the condition usually becomes more difficult to treat, and the number of available treatment options may decrease. The patient experts also highlighted the significant impact the condition can have on quality of life, affecting all aspects of life for people with the condition, and for their families and carers. The committee acknowledged that multiple myeloma is a chronic, incurable and highly individual condition that can have a negative impact on quality of life for people with the condition, and for their families and carers.

Clinical management

Treatment pathway

3.2 First-line treatment options for people with multiple myeloma depend on whether an autologous stem cell transplant (ASCT) is suitable. NICE recommends the following treatments as first-line options when an ASCT is unsuitable:

- thalidomide or bortezomib, plus an alkylating agent and a corticosteroid (see

NICE's technology appraisal guidance on bortezomib and thalidomide for the first-line treatment of multiple myeloma, from here TA228)

- bortezomib, cyclophosphamide and dexamethasone (Bor-Cyclo-Dex) or bortezomib, melphalan and prednisone (Bor-Mel-Pred)
- lenalidomide plus dexamethasone (Len-Dex; see NICE's technology appraisal guidance on lenalidomide plus dexamethasone for previously untreated multiple myeloma)
- daratumumab plus lenalidomide and dexamethasone (Dar-Len-Dex; see NICE's technology appraisal guidance on daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable, from here TA917)
- isatuximab plus bortezomib, lenalidomide and dexamethasone (Isa-Bor-Len-Dex; see NICE's technology appraisal guidance on isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable, from here TA1098).

The patient experts explained that multiple myeloma typically becomes resistant to treatment over time. They emphasised that the most effective treatments should be used at first line because, with each relapse, subsequent treatments are often less effective and harder to tolerate. They acknowledged that an ASCT is generally thought to be the most effective treatment option. But they noted that, when an ASCT is unsuitable, treatments that can deliver comparable outcomes are particularly important. The committee acknowledged the complex and evolving treatment pathway for multiple myeloma. It concluded that there is a need for safe and effective first-line treatment options when an ASCT is unsuitable.

Positioning of daratumumab with bortezomib, lenalidomide and dexamethasone

3.3 For this evaluation, the company positioned daratumumab with bortezomib, lenalidomide and dexamethasone (Dar-Bor-Len-Dex) as a first-line treatment option for multiple myeloma only when an ASCT is unsuitable. The committee recalled that the marketing authorisation for Dar-Bor-Len-Dex is broader,

covering 'adult patients with newly diagnosed multiple myeloma'. It was aware of an ongoing NICE evaluation of Dar-Bor-Len-Dex for untreated multiple myeloma when an ASCT is suitable, which would also cover part of the population within the marketing authorisation (see section 3.5). For untreated multiple myeloma when an ASCT is unsuitable, the company explained that the relevant comparators were:

- Dar-Len-Dex, current standard care in the NHS that most people would have when an ASCT is unsuitable and the main comparator
- Len-Dex, mainly used when a triplet regimen is unsuitable or when people prefer an oral treatment option
- bortezomib combinations (Bor-Mel-Pred and Bor-Cyclo-Dex), for a small proportion of people.

The company explained that Isa-Bor-Len-Dex was initially excluded from its original submission because, in TA1098, it had only been recommended under routine commissioning in September 2025. So, it was unlikely to represent established NHS practice at the time of the first committee meeting in December 2025. At clarification, the company provided analyses that included Isa-Bor-Len-Dex as a comparator. The clinical experts explained that Dar-Len-Dex is currently the main first-line treatment for untreated multiple myeloma when an ASCT is unsuitable. They explained that they would like to offer Isa-Bor-Len-Dex. But they noted that it is not yet widely used in NHS practice, and hoped that most NHS trusts would be able to offer it within the next year. The NHS Cancer Drugs Fund clinical lead agreed that Isa-Bor-Len-Dex is not yet widely used, but thought that it would be inappropriate to exclude it as a comparator. The clinical experts explained that isatuximab is administered intravenously and more frequently than daratumumab, which is administered subcutaneously. So, isatuximab is more resource intensive to deliver. The NHS Cancer Drugs Fund clinical lead agreed that there would be additional resource use associated with the administration of isatuximab treatment, such as increased nurse time. The committee thought that isatuximab's additional resource use should be captured in the model. It concluded that the relevant comparators for this evaluation are Dar-Len-Dex and Isa-Bor-Len-Dex.

Clinical evidence

Key clinical trial: CEPHEUS

3.4 The clinical-effectiveness evidence for Dar-Bor-Len-Dex came from CEPHEUS, an ongoing, phase 3, randomised, open-label, multicentre trial comparing Dar-Bor-Len-Dex (n=197) with Bor-Len-Dex (n=198). It included 395 people with newly diagnosed, untreated multiple myeloma for whom an ASCT was not planned as initial therapy. Stratification factors at randomisation included age and ASCT eligibility. The company categorised the trial population as ASCT-ineligible (n=289, 73%) or ASCT-declined or deferred (n=106, 27%). The ASCT-ineligible subgroup was defined as people aged 18 to 70 years with comorbidities that made an ASCT unsuitable, or people over 70 years. The ASCT-declined or -deferred subgroup included people 70 years or under who had declined a transplant. The company thought that the ASCT-declined or -deferred subgroup was outside its target ASCT-ineligible population and not relevant to the decision problem (see section 3.3). This was based on feedback from UK clinical experts to the company, who advised that this subgroup did not represent a distinct clinical population in UK clinical practice (see section 3.5). The primary outcome was overall minimal residual disease (MRD) negativity rate, a measure of residual tumour cells in the bone marrow. Key secondary outcomes included progression-free survival (PFS) and overall survival (OS). The company presented results from its latest data cut (May 2024), initially only for the ASCT-ineligible subgroup. In response to the draft guidance consultation, it also presented results for the intention-to-treat (ITT) population, which included the ASCT-declined or -deferred subgroup (see section 3.7).

ASCT-declined or -deferred subgroup

3.5 The committee considered whether people who declined or deferred an ASCT should be included within the ASCT-ineligible population, that is people for whom an ASCT is not suitable. It also considered whether the ASCT-declined or -deferred subgroup from CEPHEUS was representative of the NHS population that would have Dar-Bor-Len-Dex. The clinical experts explained that, in NHS practice, people generally follow 1 of 2 distinct treatment pathways:

ASCT-eligible or ASCT-ineligible. They noted that relatively few people would decline or defer an ASCT if it is considered suitable. Decisions to decline may be influenced by factors such as comorbidities or practical considerations, for example, time off work for recovery. They also explained that people who decline an ASCT would not usually later revisit this decision, and, even if they did, an ASCT may no longer be suitable. The clinical experts also highlighted that there is no established or funded NHS treatment pathway for people who defer an ASCT. So, they expect that people who decline or defer an ASCT are likely to be treated within the ASCT-ineligible pathway and have similar outcomes.

The committee noted that not including the ASCT-declined or -deferred subgroup in this evaluation could exclude some people with untreated multiple myeloma covered by the marketing authorisation (see section 3.3). So, it requested clinical- and cost-effectiveness analyses for the full CEPHEUS ITT population, alongside those for the ASCT-ineligible subgroup. In response to the draft guidance consultation, the company presented baseline characteristics and analyses for the ITT population, but maintained its preference for using only the ASCT-ineligible subgroup. It thought that this subgroup was more representative of the NHS population that would have Dar-Bor-Len-Dex. This was because the ASCT-declined or -deferred subgroup in CEPHEUS:

- was younger and fitter, and likely to have better outcomes
- had non-biological reasons for deferral, such as clinician or patient choice
- was disproportionately affected by COVID-19, with recruitment concentrated in Brazil and Poland
- did not include anyone from the UK and would limit generalisability to the NHS.

The company highlighted that the median age across trials was lowest in the CEPHEUS ASCT-declined or -deferred subgroup (under 70 years) compared with the ASCT-ineligible (72 years) and ITT (70 years) populations. The committee noted that people in the CEPHEUS ASCT-declined or -deferred subgroup were younger and would be expected to have better outcomes. But it noted that this group showed worse outcomes in the trial. The clinical experts thought that the CEPHEUS ASCT-declined or -deferred subgroup was unlikely to be representative of people in the NHS for whom an ASCT

would be unsuitable. They explained that ASCT eligibility is not usually determined by a strict age cutoff, but by the ability to tolerate high-dose melphalan, a toxic component of the procedure. They noted that this approach to assessing eligibility has been consistent over time and across multiple myeloma trials.

The committee noted that clinical advice to the EAG suggested the baseline characteristics of the CEPHEUS ASCT-ineligible subgroup did not fully reflect the NHS population, which is likely to be older and include a higher proportion of males (see section 3.8). It acknowledged that people in the NHS who decline or defer an ASCT would follow the ASCT-ineligible pathway. But it thought that the CEPHEUS ASCT-declined or -deferred subgroup was probably not representative of the NHS ASCT-ineligible population. It particularly thought this because decisions to have an ASCT was influenced by factors unlikely to apply in the NHS now (for example, COVID-19-related treatment decisions). The committee concluded that the CEPHEUS ASCT-ineligible subgroup was the most appropriate to inform decision making.

Indirect treatment comparisons

3.6 The company provided several indirect treatment comparison (ITC) approaches to estimate the clinical effectiveness of Dar-Bor-Len-Dex compared with Dar-Len-Dex and Isa-Bor-Len-Dex in the ASCT-ineligible population. For its base cases, the company preferred:

- for the comparison with Dar-Len-Dex, an inverse probability of treatment weighting (IPTW) ITC using individual patient data from the CEPHEUS and MAIA (Dar-Len-Dex) trials, adjusted for COVID-19 and 11 covariates (including age, sex and Eastern Cooperative Oncology Group performance status), in line with NICE's decision support unit technical support document 18 on methods for population-adjusted indirect comparisons
- for the comparison with Isa-Bor-Len-Dex, a fixed-effects network meta-analysis (NMA), unadjusted for COVID-19, including 11 studies, although the comparison was mainly informed by the CEPHEUS and IMROZ (Isa-Bor-Len-Dex) trials.

The company explained that the timing of study recruitment for CEPHEUS coincided with the peak of the COVID-19 pandemic and so some participants died from COVID-19 (the company considers the exact data to be confidential, so it cannot be reported here). It preferred to adjust for these deaths in its IPTW ITC analyses only. It did not adjust for COVID-19 deaths in the Isa-Bor-Len-Dex comparison. This was because, although both CEPHEUS and IMROZ were both ongoing during the COVID-19 pandemic, the company did not have access to individual patient data from IMROZ. So, it thought that it would be inappropriate to censor data in the Dar-Bor-Len-Dex arm only. The committee agreed with the company's differing approaches to adjusting for COVID-19 deaths in the 2 comparisons. It noted that adjustment for COVID-19 deaths may have been appropriate. But it thought that it could have introduced bias by excluding people at higher risk of death or adverse events. This could have resulted in a relatively 'fitter' population with potentially better outcomes. It also noted that removing COVID-19 deaths in CEPHEUS but not in IMROZ would introduce additional uncertainty. The committee noted that both CEPHEUS and MAIA were adjusted for COVID-19 deaths, so any potential bias would apply to both trials. But it thought that the extent of any differential impact remained uncertain.

The EAG noted that, overall, the statistical methods used in the IPTW ITC and NMA were appropriate. The committee acknowledged that the range of approaches the company presented (including IPTW ITC, and matching-adjusted indirect comparison) showed a consistent direction of effect across outcomes for both comparisons. But it also noted that the magnitude of effect varied.

The committee noted that it would usually prefer an approach that maintains randomisation, such as an NMA. But it thought that the IPTW ITC was more appropriate for the comparison with Dar-Len-Dex because the key linking trial in the NMA (SWOG S0777) introduced substantial uncertainty. This was because SWOG S0777 was older so had limited generalisability to current NHS practice. It also used a proxy population and probably had imbalances in important effect modifiers that could not be adjusted for. The committee also noted evidence provided by the company in response to the draft guidance consultation showing that the proportional hazards assumption in the NMA was violated.

For the comparison with Isa-Bor-Len-Dex, the committee was reassured by the consistency of results. It agreed that the fixed-effects NMA was appropriate because the key trials (CEPHEUS and IMROZ) were directly linked. It thought that a random-effects NMA added unnecessary uncertainty. The committee acknowledged the analyses presented for the ITT population, which were broadly consistent with those for the ASCT-ineligible subgroup. It concluded that the company's base-case approaches for the ITCs in the ASCT-ineligible population were appropriate for decision making.

Clinical-effectiveness results

3.7 From CEPHEUS (see section 3.4), in the ASCT-ineligible subgroup, compared with Bor-Len-Dex, with Dar-Bor-Len-Dex:

- There was a statistically significant higher proportion of people with MRD negativity (60.4% with Dar-Bor-Len-Dex compared with 39.3% with Bor-Len-Dex; odds ratio 2.365; 95% confidence interval [CI] 1.47 to 3.80).
- In the COVID-19-unadjusted analyses, there was a statistically significant improvement in PFS (hazard ratio [HR] 0.51; 95% CI 0.35 to 0.74) but no statistically significant difference in OS (HR 0.66; 95% CI 0.42 to 1.03).
- In the COVID-19-adjusted analyses, there were statistically significant improvements in both PFS (the company considers the exact data to be confidential, so it cannot be reported here) and OS (HR 0.55; 95% CI 0.34 to 0.90).

From the ITCs (see section 3.6), in the ASCT-ineligible subgroup, with Dar-Bor-Len-Dex:

- Compared with Dar-Len-Dex, there were statistically significant improvements in PFS (HR 0.55; 95% CI 0.38 to 0.79) and OS (HR 0.63; 95% CI 0.41 to 0.98) in the COVID-19-adjusted analyses.
- Compared with Isa-Bor-Len-Dex, there was no statistically significant differences in PFS (HR 0.85; 95% CI 0.52 to 1.38) or OS (HR 0.85; 95% CI 0.48

to 1.49) in the COVID-19-unadjusted analyses.

The committee noted that CEPHEUS is ongoing (see section 3.4) and that median PFS and OS for Dar-Bor-Len-Dex had not yet been reached. It concluded that Dar-Bor-Len-Dex is likely to be an effective treatment option for untreated multiple myeloma when an ASCT is unsuitable, particularly compared with Dar-Len-Dex. But it also concluded that that there were no statistically significant differences in PFS and OS compared with Isa-Bor-Len-Dex.

Economic model

Company's modelling approach

3.8 The company provided a cohort-based partitioned survival model to estimate the cost effectiveness of Dar-Bor-Len-Dex compared with Dar-Len-Dex and Isa-Bor-Len-Dex. The model included 3 health states: preprogression, postprogression and death. The probability of being in each health state was estimated using extrapolated PFS and OS curves (see section 3.9). The model included a cycle length of 4 weeks with a half-cycle correction over a lifetime horizon. In its original base case, the company used baseline characteristics from the ASCT-ineligible subgroup of CEPHEUS (the company considers the data to be confidential, so it cannot be reported). The EAG preferred to use a mean age of 75 years and a male proportion of 55%. This was based on clinical advice that people with untreated multiple myeloma in the NHS are likely to be older and include a higher proportion of males. These values were consistent with real-world data from England from the National Cancer Registration and Analysis Service (2015 to 2022; the exact data is confidential and so cannot be reported here). The committee thought the National Cancer Registration and Analysis Service data better reflected the NHS population, and noted that they were consistent with the EAG's preferred assumptions. In response to the draft guidance consultation, the company updated its base case to include the EAG's preferred population baseline characteristics. The committee concluded that the company's updated model was acceptable for decision making.

PFS and OS extrapolation

3.9 In its original base case, the company fitted independent extrapolations to patient-level data for the Dar-Bor-Len-Dex and Dar-Len-Dex treatment arms. For Dar-Bor-Len-Dex, COVID-19-adjusted PFS and OS average treatment effect-weighted Kaplan–Meier data from the ASCT-ineligible subgroup of CEPHEUS was used. For Dar-Len-Dex, COVID-19-adjusted PFS and OS average treatment effect-weighted Kaplan–Meier data from MAIA (less than 80 years) was used. Extrapolations for Isa-Bor-Len-Dex were generated by applying the PFS and OS hazard ratio from the NMA to the Dar-Bor-Len-Dex extrapolations. The committee recalled that median PFS and OS had not yet been reached in CEPHEUS (see section 3.7). It thought that this increased uncertainty in the long-term extrapolations, particularly given the use of independently fitted models. To explore this uncertainty, it requested scenario analyses using alternative baseline OS curves with relative treatment effects applied. For example, using Systemic Anti-Cancer Therapy (SACT) data for Dar-Len-Dex as the baseline OS curve, with the relevant hazard ratio applied. It also thought that, for independently fitted extrapolations, plots of the implied hazard ratios between the modelled arms over time would be informative.

In response to the draft guidance consultation, the company explained that no SACT data was available and instead provided a scenario using the second-best-fitting curves as an alternative OS baseline. It noted that this scenario had a small impact on the cost-effectiveness results. The company also provided the implied hazard ratios between the independently fitted Dar-Bor-Len-Dex and Dar-Len-Dex extrapolations for PFS and OS. The committee noted that the average implied hazard ratios were less favourable, and so more conservative, than those from the ITC across the lifetime time horizon. It thought that the company's modelling approach was inherently conservative and that this reduced uncertainty in the long-term survival estimates.

Extrapolation of time-to-treatment discontinuation for Isa-Bor-Len-Dex

3.10 In its base case, the company assumed that time-to-treatment discontinuation (TTD) for Isa-Bor-Len-Dex was equal to that of Dar-Bor-Len-Dex. This was

because there was insufficient published TTD data for Isa-Bor-Len-Dex, so an ITC with Dar-Bor-Len-Dex was not feasible. The company thought that this was a reasonable assumption, given that both isatuximab and daratumumab are anti-CD38 quadruplet regimens. The company also provided a scenario in which TTD for Isa-Bor-Len-Dex was shorter. This was, derived by applying the COVID-19-unadjusted PFS hazard ratio to the Dar-Bor-Len-Dex TTD curve, ensuring consistency between PFS and TTD. It thought that a shorter TTD for Isa-Bor-Len-Dex was plausible. This was because of the greater treatment burden associated with intravenous administration, including longer administration times, additional hospital visits and a potentially greater adverse event burden. For example, intravenous administration for isatuximab is 75 minutes to 4 hours (based on isatuximab's summary of product characteristics) compared with daratumumab's subcutaneous injection, which takes around 3 to 5 minutes. Isatuximab is also associated with 15 additional hospital visits in the first 2 years of treatment. The clinical experts agreed about the potential impact on quality of life of the longer administration time and adverse event profile of isatuximab. But they thought that it was not unreasonable to assume that Isa-Bor-Len-Dex would have a shorter TTD.

In response to the draft guidance consultation, a stakeholder suggested that TTD for Isa-Bor-Len-Dex could be modelled using the Dar-Len-Dex TTD curve. This was based on TA1098, in which the committee accepted an assumption of equal TTD for these treatments. The EAG noted that the committee for TA1098 had raised concerns about a longer gap between stopping treatment and disease progression for Isa-Bor-Len-Dex. It also noted that the unadjusted Isa-Bor-Len-Dex population from IMROZ had a similar median TTD to the modelled Isa-Bor-Len-Dex TTD when applying the company's scenario using the unadjusted PFS hazard ratio to the Dar-Bor-Len-Dex TTD curve. The committee noted that the assumption of equal TTD in TA1098 was based on matched populations from IMROZ and MAIA. It had concerns about using TTD data for Dar-Len-Dex from MAIA because of potential differences in populations between MAIA and CEPHEUS. It thought that the comparison of TTD across the trials was naive. Taking all the evidence into account, the committee thought that TTD may plausibly be shorter for Isa-Bor-Len-Dex, given the issues related to treatment administration. It concluded that the company's scenario using the COVID-19-unadjusted PFS hazard ratio should be used to estimate the TTD for Isa-Bor-Len-Dex.

Proportion having second-line treatment

3.11 In its model, the company derived the proportion of people moving on to second-line treatment based on trial data:

- CEPHEUS for Dar-Bor-Len-Dex (the company considers the data to be confidential, so it cannot be reported here)
- MAIA for the Dar-Len-Dex arm (81%)
- IMROZ for Isa-Bor-Len-Dex (72%).

The company explained that fewer people moved on to second-line treatment in CEPHEUS, reflecting improved PFS benefit with Dar-Bor-Len-Dex. It also explained that people would be older at disease progression, so less likely to have subsequent treatments. The committee noted that the company applied a fixed proportion. The committee thought that this was an oversimplification. In CEPHEUS, a slower transition to second-line treatment would have been expected initially. But the proportion of people having second-line treatment would likely increase over time, particularly given that median OS and PFS had not yet been reached. So, the committee thought that the company's proportion of people moving on to second-line treatment may have been underestimated.

Clinical advice to the EAG was that it was unlikely that the proportion moving on to second-line treatment after Dar-Bor-Len-Dex would be as low as the company's estimate. So, the EAG preferred to assume a higher proportion (75%) moving onto second-line treatment for both Dar-Bor-Len-Dex and Isa-Bor-Len-Dex. It also noted that more mature data would reduce uncertainty. The clinical experts explained that age is an important factor in determining eligibility for second-line treatments. But they added that people with a complete response may not need subsequent treatment. They suggested that this may be more likely with Dar-Bor-Len-Dex than with Dar-Len-Dex, although it was uncertain how this compared with Isa-Bor-Len-Dex.

Overall, the committee thought that the company's estimate was likely to have underestimated second-line treatment use, particularly because it was based on an earlier data cut from CEPHEUS. It also noted the limitations of

applying a fixed proportion to a time-dependent variable. It recalled that the ITC between Dar-Bor-Len-Dex and Isa-Bor-Len-Dex did not show a statistically significant difference in PFS (see section 3.7). The committee also thought that, given they are similar 4-drug combinations, it would be reasonable to assume the same rate of subsequent therapy. So, it thought that the EAG's assumption of 75% going onto second-line treatment after Dar-Bor-Len-Dex and after Isa-Bor-Len-Dex was appropriate for decision making. In response to the draft guidance consultation, the company updated its base case to assume that 75% of people had second-line treatment after Dar-Bor-Len-Dex and Isa-Bor-Len-Dex. The committee concluded that the company's updated approach was appropriate for decision making.

Distribution of subsequent treatments

3.12 In its base case, the company assumed the same distribution of second- and third-line subsequent treatments for Dar-Bor-Len-Dex, Dar-Len-Dex and Isa-Bor-Len-Dex. These distributions were informed by a UK clinical expert advisory board of 5 haematologists in May 2025. The EAG thought that subsequent treatment distributions would differ depending on the first-line treatment used. It preferred to use different distributions at second and third line based on clinical expert opinion. At the second committee meeting, the clinical experts thought that second-line treatment distributions would be broadly similar regardless of prior first-line regimen. Key differences between the EAG's and company's base-case assumptions were:

- at second line, a lower proportion of people having Bel-Bor-Dex (74% compared with 87.5% in the company's base case)
- at second line, some use of carfilzomib plus lenalidomide and dexamethasone (Car-Len-Dex; 4%), which was excluded from the company's base case
- at third line, a lower proportion having selinexor plus bortezomib and dexamethasone (Sel-Bor-Dex; 10% compared with 41.2% in the company's base case), reflecting limited availability
- at third line, higher use of panobinostat plus bortezomib and dexamethasone and cyclophosphamide-based regimens in the EAG's base case.

The clinical experts noted that selinexor is still commonly used, particularly at third line. They also noted that uptake of Bel-Bor-Dex varies across the NHS. They explained that, based on current practice, Bel-Bor-Dex use would be lower than the 87.5% assumed in the company's base case. But they thought that this would likely increase over time as availability improves and healthcare professionals become more familiar with managing its associated toxicities. They also thought that Bel-Bor-Dex is likely to become the most commonly used option at second line. But the NHS England Cancer Drugs Fund lead noted that a proportion as high as 87.5% would imply near-universal use, which is unlikely. The committee thought that the distributions of subsequent treatments at second and third line were uncertain. So, it requested additional evidence to inform what would be expected in NHS practice, including validation of the distributions used. It noted that this could include the use of SACT data, particularly to inform the selinexor use at third line. In response to the draft guidance consultation, the company noted that:

- the EAG's preferred second-line distribution was not clinically plausible and may not align with NICE's recommendations
- robust SACT data following first-line Dar-Len-Dex or Dar-Bor-Len-Dex are not available
- clinical expert opinion remained the most appropriate source, given the long PFS of first-line treatments and rapidly evolving treatment pathways.

The company provided additional scenarios informed by NHS pharmacy and ePrescribing datasets (VSTx), based on data available in December 2025 (the company considers the data to be confidential, so it cannot be reported here). It noted that this data reflected the prevalent population rather than new patients, did not link second-line treatment to prior first-line treatment and did not provide information for third-line treatment. The company provided 2 scenarios:

- scenario 1: 50% had Bel-Bor-Dex at second line, with remaining treatments reweighted
- scenario 2: based on VSTx dataset, reflecting observed treatment shares.

The NICE technical team noted that the company had used a limited subset of VSTx data, and provided additional scenarios based on the full dataset:

- scenario 3: redistribution of people having Dar-Bor-Dex to Bel-Bor-Dex
- scenario 4: redistribution of people having Dar-Bor-Dex across all second-line options based on observed weighting.

The company noted that there was insufficient data to inform third-line treatment distributions. The NHS Cancer Drugs Fund clinical lead provided BlueTeQ data on trends in second-line treatments over 6 months in 2025. But they noted that these data included both ASCT-eligible and ASCT-ineligible populations and had no linkage to prior treatments. The reported proportions were 52.1% for Dar-Bor-Dex (n=903), 16.8% for Car-Len-Dex (n=291), 13.8% for Bel-Bor-Dex (n=239), 12.8% for Sel-Bor-Dex (n=221), 4.6% for Car-Dex (n=79) and less than 1.0% for Len-Dex. The clinical experts thought that Bel-Bor-Dex is likely to become a preferred second-line option, despite challenges such as ocular toxicity, which require additional monitoring. They noted that other treatments, including selinexor- and carfilzomib-based regimens, are limited by tolerability and toxicity, which may restrict their use to fitter people who can tolerate them. The clinical experts explained that scenario 3 was the most likely to reflect subsequent treatment proportions in NHS practice. The committee thought that subsequent treatment distributions at second and third line were still uncertain. It thought that Bel-Bor-Dex use at second line is likely to increase over time, but that the proportion assumed in the company's base case was too high for current NHS practice. So, the committee thought that scenario analyses informed by available real-world data and clinical input were appropriate, while recognising the limitations of the evidence. It concluded that scenario 3, with a lower proportion of Bel-Bor-Dex use than the company's base case of 87.5%, was preferred for decision making.

Subcutaneous administration costs

3.13 In its base case, the company used a cost code for subcutaneous administration that included nurse time only and excluded chair time (N10AF; Specialist nursing, cancer related, adult, face to face; National Schedule of NHS Costs 2023 to

2024; £115.36). In response to the draft guidance consultation, a stakeholder highlighted that a cost code including both nurse and chair time (SB12Z; day-case chemotherapy delivery; National Schedule of NHS Costs 2023 to 2024; £152) had been applied in TA1098. The NHS Cancer Drugs Fund clinical lead confirmed that SB12Z was more appropriate for subcutaneous administration. The committee concluded that a cost of £152 based on SB12Z should be applied in the model.

Severity

3.14 NICE's methods on conditions with a high degree of severity did not apply.

Cost-effectiveness estimates

Committee's preferred assumptions

3.15 The committee noted its preferred assumptions, which were:

- including Dar-Len-Dex and Isa-Bor-Len-Dex as relevant comparators (see section 3.3)
- using data from the ASCT-ineligible population only (see section 3.5)
- using an IPTW ITC, adjusted for COVID-19, to inform the clinical effectiveness of the Dar-Len-Dex comparison (see section 3.6)
- using a fixed-effects NMA, unadjusted for COVID-19, to inform the clinical effectiveness of the Isa-Bor-Len-Dex comparison (see section 3.6)
- using model baseline characteristics of 75 years and 55% male (see section 3.8)
- applying the company's scenario using the COVID-19-unadjusted PFS hazard ratio to estimate Isa-Bor-Len-Dex's TTD (see section 3.10)
- 75% of people move on to second-line subsequent treatment after Dar-Bor-

Len-Dex and Isa-Bor-Len-Dex (see section 3.11)

- applying NICE technical team's scenario 3 distribution of subsequent treatments based on full VSTx dataset (see section 3.12)
- applying a cost of £152 based on SB12Z for subcutaneous administration (see section 3.13).

Acceptable ICER

3.16 NICE's manual on technology appraisal and highly specialised technologies guidance notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £25,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects, including uncaptured health benefits. The committee noted some uncertainty remained, specifically:

- the trial is still ongoing, and median PFS and OS have not been reached (see section 3.4 and section 3.7)
- uncertainties in modelling the proportion of people having second-line treatment (see section 3.11)
- uncertainties in the distribution of second- and third-line treatments (see section 3.12).

So, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£25,000 to £35,000 per QALY gained).

Company and EAG cost-effectiveness estimates

3.17 The committee considered the cost effectiveness of Dar-Bor-Len-Dex compared with Dar-Len-Dex and Isa-Bor-Len-Dex. After the second committee meeting, the company updated its commercial offering and the cost-effectiveness estimates

using all of the committee's preferred assumptions were provided. The exact ICERs cannot be reported here because some prices are confidential. The committee noted that there was little difference between the probabilistic and deterministic ICERs for the comparison with Dar-Len-Dex. It also noted that the OS, PFS and TTD hazard ratios for Isa-Bor-Len-Dex are not included in the probabilistic sensitivity analyses. So, it preferred the deterministic ICERs to inform decision making. Using the committee's preferred assumptions from the second committee meeting, the ICERs were within the range that NICE considers a cost-effective use of NHS resources for this evaluation (see section 3.16).

Other factors

Equality

3.18 The committee did not identify any equality issues.

Uncaptured benefits

3.19 The committee considered whether there were any uncaptured benefits of Dar-Bor-Len-Dex. In response to the draft guidance consultation, patient groups highlighted the impact of treatment administration on quality of life, noting that subcutaneous daratumumab is more convenient than intravenous isatuximab. They explained that daratumumab avoids the need for cannulation, requires less time in clinic, and may allow for community or home administration. Isatuximab, on the other hand, requires hospital attendance for intravenous infusion. They also noted that daratumumab has a less intensive dosing schedule, with monthly administration after 24 weeks, compared with more frequent dosing over a longer period with isatuximab. The patient groups emphasised that ease of administration could reduce the physical and psychological burden of treatment, including disruption to work, family life and daily activities, and travel and financial costs. They added that it may improve independence and sense of normality. They also thought that the quality-of-life measures used in the model may have underestimated quality-of-life benefits. This was because they did not fully capture the cyclical anxiety associated with relapse or the wider emotional

burden on carers and families. The committee noted that disutility associated with intravenous administration had not been included in the model. It concluded that there were uncaptured benefits associated with daratumumab because it can be delivered subcutaneously, which may be more convenient than intravenous treatments like isatuximab.

Conclusion

Recommendation

3.20 The committee noted that Dar-Bor-Len-Dex improved PFS and OS in the COVID-19-adjusted analyses compared with Dar-Len-Dex. But it also noted that, when compared with Isa-Bor-Len-Dex, the differences were not statistically significant. It also recalled that median PFS and OS from CEPHEUS had not been reached, and that there was additional uncertainty associated with the modelling of subsequent treatments. But it recognised the uncaptured benefits of a subcutaneous quadruplet regimen at first line. Using the committee's preferred assumptions, the ICERs were within the range that NICE considers a cost-effective use of NHS resources (see section 3.16). So, Dar-Bor-Len-Dex can be used for untreated multiple myeloma in adults when an ASCT is unsuitable.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has multiple myeloma and an autologous stem cell transplant is unsuitable and the healthcare professional responsible for their care thinks that daratumumab with bortezomib, lenalidomide and dexamethasone is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley
Chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

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Emily Crowe
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